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Review

Global expansion of chikungunya virus: mapping the 64-year history

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SUMMARY

Chikungunya virus (CHIKV) is a mosquito-transmitted alphavirus that is emerging as a global threat because of the highly debilitating nature of the associated disease and unprecedented magnitude of its spread. Chikungunya originated in Africa and has since spread across the entire globe causing large numbers of epidemics that have infected millions of people in Asia, the Indian subcontinent, Europe, the Americas, and Pacific Islands. Phylogenetic analysis has identified four different genotypes of CHIKV: Asian, West African, East/Central/South African (ECSA), and Indian Ocean Lineage (IOL). In the absence of well-designed epidemiological studies, the aim of this review article was to summarize the global epidemiology of CHIKV and to provide baseline data for future research on the treatment, prevention, and control of this life-threatening disease.

Contents

Introduction

The chikungunya virus (CHIKV) is an enveloped, spherical, single-stranded positive-sense RNA alphavirus belonging to the family *Togaviridae*. The genome size is approximately 12 kb and it consists of two open reading frames. The genome is cleaved into four non-structural proteins (nsP1, nsP2, nsP3, and nsP4) and five structural proteins (C, E3, E2, 6 K, and E1).[1,2] The glycoproteins E1 and E2 both play an important role in viral replication. The E1 glycoprotein is important for membrane fusion and the E2 glycoprotein allows the virus to enter the cell through endocytosis.[3] CHIKV is transmitted by mosquitoes of the *Aedes* species, specifically *Aedes albopictus*,*Aedes aegypti*, and *Aedes polynesiensis*.[4–6]

High fever, headache, myalgia, arthralgia, polyarthralgia, hemorrhage, and rash are the typical clinical signs of CHIKV fever. Several studies have reported that arthralgia persists for longer periods of time and causes severe pain in older people, as well as in diabetic patients. Individuals with impaired renal function and alcoholic hepatopathy suffer the most. Significant numbers of neonates acquire CHIKV infection from their mothers due to vertical transmission.[7] Accumulating evidence shows the occurrence of neurological complications as a consequence of CHIKV infection.[8–10] Animal-based experimental studies have demonstrated that CHIKV mainly targets fibroblast cells and may also enter into monocytes and Kupffer cells of the liver. Replication of the virus depends on defective type 1 interferon (IFN)-signaling and the neonate's age.[7,11]

Phylogenetic analysis has revealed four different genotypes of CHIKV on the basis of geographical regions. The West African

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genotype consists of isolates from Senegal and Nigeria. The East/Central/South African (ECSA) genotype is another genotype enzootic in Africa. Isolates from Asian countries are included in the Asian genotype. The more recent Indian Ocean Lineage (IOL) genotype spread from the Comoros islands in 2004 and resulted in severe epidemics in Southeast Asia and India during the years 2005–2008[12,13] (Figure 1).

E1-A226V and E2-L210Q mutations have been found to cause a dramatic increase in the infectivity of CHIKV, and the transmission of CHIKV has spread to Europe and the Americas because of the widespread distribution of the vectors *A. aegypti* and *A. albopictus*.[15] Several studies have suggested that the highly competent vector *A. albopictus* was responsible for the chikungunya outbreak on La Réunion Island in 2005–2006. CHIKV can be detected easily using several different methods: viral culture, reverse transcriptase PCR (RT-PCR), hemagglutination inhibition test (HAI), and ELISA.[16–18] The diagnosis of chikungunya has been challenging due to the similarity of the clinical symptoms to those of dengue. In order to overcome this challenge, researchers have used multiplex real-time RT-PCR assays that quantitate and detect RNA for all CHIKV serotypes and dengue virus (DENV).[19] It has also been reported that patients infected with CHIKV are more likely to experience a maculopapular rash, arthritis/arthralgia, and conjunctival injection.[20] Moreover, a white blood cell count $\geq 5.0 \times 10^9$ cells/l, skin rash during fever, and specific antigen testing form the basis of the differential diagnosis of CHIKV and DENV[21,22] (Figure 2).

There is currently no available vaccine for CHIKV. Therefore preventive measures should be practiced to mitigate the risk of disease, and supportive therapy is equally important as it lessens the severity of the disease.[23]

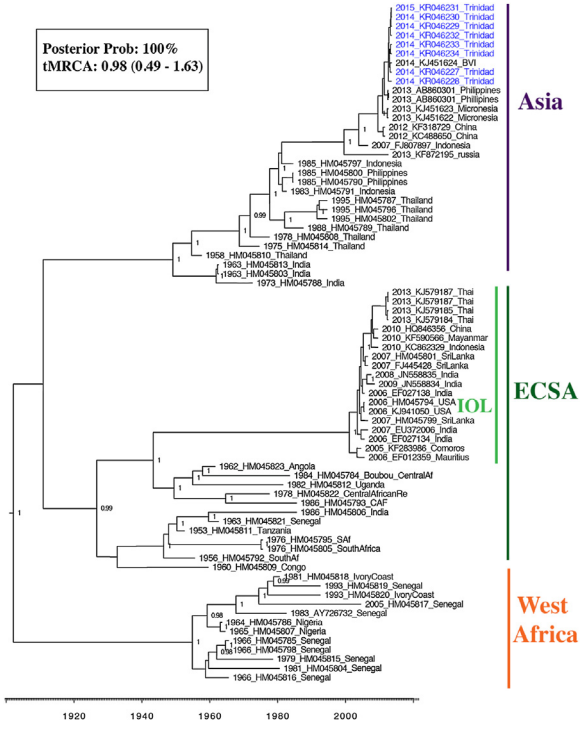

Figure 1. Maximum clade credibility (MCC) phylogeny based on the complete coding region of 74 chikungunya virus sequences. The chikungunya virus isolated during an epidemic that occurred in the Indian Ocean in 2005 and 2006 represented a novel ECSA with a mutation from alanine to valine at position 226 in the E1 envelope glycoprotein gene (E1-A226V); this was subsequently described as the Indian Ocean Lineage (IOL).[14]

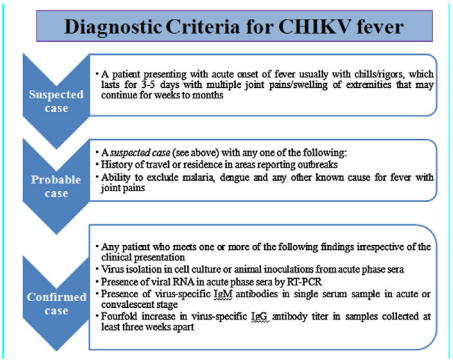

Figure 2. Diagnostic criteria for chikungunya virus.

CHIKV has spread to almost 40 countries worldwide. This review was performed to discuss the global epidemiology of CHIKV because of its high morbidity and explosive onset over the last two decades.

The epidemiological pattern of CHIKV includes sporadic and epidemic cases in West Africa, from Cameroon to Senegal, as well as in several other African countries (Central African Republic, South Africa, Angola, Nigeria, Democratic Republic of the Congo, South Africa, Malawi, Guinea, and Uganda). A number of epidemics occurred in the 1960s and 1990s, followed by major outbreaks occurring intermittently with an inter-epidemic period ranging from 7 to 20 years.[23] CHIKV is now distributed worldwide because of the prevalence of the vectors and their efficiency in transmitting the virus. Another possible cause of the spread of CHIKV is travel. Travel patterns have increased the importation of the virus into new geographical regions via viremic people.[24]

Epidemiology and global expansion

In Africa, CHIKV was first reported in Tanzania in 1952. This was followed by several other epidemics in Central African Republic, Guinea, Burundi, Angola, Uganda, Malawi, Nigeria, Democratic Republic of the Congo, and several other states. During the 1960s to the 1990s, outbreaks were recorded in the Democratic Republic of the Congo, Central African Republic, Malawi, Uganda, Burundi, Angola, Guinea, South Africa, and Nigeria. Almost half a million cases were reported in June 2004 in an outbreak that occurred in *Lamu Atoll*, Kenya. The seroprevalence rate was 70%[25] and increased abruptly to 75%, followed by migration to nearby regions including Mauritius, Seychelles, Comoros, and La Réunion Island up until March–April 2005. Several other epidemics occurred on all of the southwestern Indian Ocean islands except Madagascar during the years 2005 to 2007. By January 2006, significant increases in the numbers of CHIKV-associated neurological complications, the mortality rate, and fetal infections were observed.[26–28] Two outbreaks were reported on La Réunion Island in 2009 and 2010.[26] In 2004, two epidemics of CHIKV infection occurred in Mombasa, one of which occurred in Lamu and infected 13 500 people.[29,30] In 2011, a CHIKV epidemic hit the Democratic Republic of the Congo (317 cases), Pool (460 cases), and Brazzaville (7014 cases). Representatives of Integrated Regional Information Networks (IRIN) reported zero mortality and an approximate count of 8000 people who were infected with CHIKV.[31–34] During 2004 to 2007, Guinea, Northern Tanzania, Sudan, Gabon, Cameroon, and Mbeya Region experienced several outbreaks.[33,35–38] The Ministry of Health and Social